Remarks/Arguments:

Information Disclosure Statement (IDS)

Applicants submit herewith an IDS. It is respectfully requested that the patent application and publications cited in the IDS be considered by the Examiner and made of record in this application.

Rejection of Claims 2, 9, 11, and 27 Under 35 U.S.C. §103(a)

The Examiner has rejected Claims 2, 9, 11, and 27 under 35 U.S.C. §103(a) over Janus *et al*, U.S. Patent Application No. 2002/0055457 in view of Curwen *et al.*, Poster EORTC-NCI-AACR, 2002, Nelson *et al.*, *BJU International* (2000), *85*(suppl. 2), p. 45-48, and Walczak *et al.*, *Expert Opinion* (2002), *11*(12), p. 1737-1748. Applicants respectfully disagree for the reasons detailed below.

On page 7 of the Office Action at point 11, the Examiner concludes the following:

> There is a reasonable expectation of success, since bisphosphonate is used in the treatment of prostate cancer and endothelin antagonist (ZD4054) in used in the treatment of prostate cancer, therefore, combining the two into a combination compound would show at least an additive effect. Further, since ZD4054 is selective for ET-A receptor, and Janus et al disclosed that bisphosphonate addition impedes bone loss, there is a reasonable expectation that the addition of the two compounds into one composition would have an additive effect. (emphasis added).

In addition, on page 9 at point 13, the Examiner further relies upon the recent Supreme Court decision *KSR International Co. v. Teleflex Inc.*, 82 U.S.P.Q.2d 1385, 1397 (2007) and concludes the following:

> . . .treating prostate cancer using combination of (N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-,2-yl]phenyl)pyridine-3-sulphonamide) and bisphosphonate

> (pamidronate or zoledronic acid) is "the product not of innovation but of ordinary skill and common sense," leading to the conclusion that invention is not patentable as it would have been obvious.

However, it is respectfully submitted that the Examiner has incorrectly applied the KSR decision to the present application.

The KSR decision and the Examination Guidelines for Determining Obviousness Under 35 U.S.C. §103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.* Federal Register / Vol. 72, No. 195 / Wednesday, October 10, 2007 / Notices, 57526, col.3, lines 8-14 of the first full paragraph clearly specify that:

> Importantly, the Supreme Court reaffirmed principles based on its precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. (emphasis added).

It is clear from KSR and the Guidelines that an invention should only be considered to be obvious when the combined elements give predictable results.

The applicants maintain that the Examiner has failed to establish even a *prima facie* argument that it would be obvious to combine ZD4054 with a bisphosphonate, for the reasons set out in the response to the last office action. However, even if there was a *prima facie* case of obviousness, it is submitted that the presently claimed combinations do not result in a predictable result.

As discussed above, the Examiner indicates that based upon her analysis of the prior art, a skilled person would expect the claimed combination to provide "at least an additive effect". However, it is respectfully submitted that the presently claimed combination surprisingly produces a far greater than additive effect.

In support of the present claims, the Examiner is asked to consider Williams et al., *Eur. J. Cancer Supplement* 2006;4(12):15 (literature reference 31 of the IDS filed on January 19, 2007 and included herein as Exhibit A for the Examiner's convenience). In this research, the effect of ZD4054 alone, pamidronate alone and a combination of ZD4054 and pamidronate on the formation of bone metastases in a mouse model are compared.

Paragraph 2, lines 9-10 and the graph of Exhibit A indicates that the effect of combining ZD4054 with pamidronate resulted in the surprising and unexpected finding that the combination actually prevented any detectable bone metastases such that no bone metastases were detected for the duration of the study. On the contrary, the use of either agent alone merely resulted in a delay in the formation of metastases (Exhibit A, paragraph 2, lines 8-9 and the graph). It is submitted that these results indicate that the effect of the combination according to the present invention is far more than additive and suggest there is a significant interaction between the ZD4054 and pamidronate giving the surprising and unexpected prevention of bone metastasis.

As discussed above, it is respectfully submitted that the correct test in KSR is that the claimed combination of elements must give a predicable result, for an invention to be considered obvious. The research detailed in Exhibit A clearly shows that the combined use of ZD4054 and pamidronate resulted in the surprising and unexpected prevention of bone metastasis formation. In contrast, the use of either agent alone merely delayed the formation of bone metastases. This could not have been predicted from the cited prior art, either alone or in combination, and the present claims are not obvious. Therefore, Applicants request that the Examiner reconsider and withdraw the rejection

Applicants believe the application is in condition for allowance, which action is respectfully requested.

Applicants have submitted herewith a fee under CFR §1.17(e) for filing a Request for Continued Examination. Although Applicants believe no additional fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 101213-1P US.

Although Applicants believe no excess claim fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 101213-1P US.

Respectfully submitted,
/Theresa Devlin/

_____

Name: Theresa Devlin
Dated: January 17, 2008

Reg. No.: 45,361
Phone No.: 781-839-4969
Global Intellectual Property, Patents,
AstraZeneca R&D Boston,
35, Gatehouse Drive,
Waltham,
MA 02451